RG71623/
RCL-317-0594

INTELLECTUAL PROPERTY INDIA

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY,
PATENT OFFICE, DELHI BRANCH,
W - 5, WEST PATEL NAGAR,
NEW DELHI - 110 008.

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application, Complete Specification*** *and* ***Drawing Sheets*** *filed in connection with Application for Patent No. 1263/Del/02 dated 16th December 2002.*

Witness my hand this 13th day of January 2004.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

1263-DEL-02

16 DEC 2002

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 7, 54 and 135 and rule 33A)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956 of 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"AN IMPROVED PROCESS FOR THE PURIFICATION OF LEVOFLOXACIN HEMIHYDRATE"**

(b) that the Complete Specification relating to this invention is filed with this application:

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. TARUN KANT SHARMA
b. PRAMOD KUMAR
c. PROSENJIT BOSE
d. YATENDRA KUMAR

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana).
INDIA.
Tel. No. (91-124) 6343126, 6342001 – 10
Fax No. (91-124) 6342027

6. Following declaration was given by the inventors in the convention country:

We, TARUN KANT SHARMA, PRAMOD KUMAR, PROSENJIT BOSE, YATENDRA KUMAR, of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a. Tarun

(TARUN KANT SHARMA)

b. Pramod Kumar

(PRAMOD KUMAR)

c. P. Bose

(PROSENJIT BOSE)

d. Yatendra Kumar

(YATENDRA KUMAR)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

a. Complete Specification (3 copies)
b. Drawings (3 copies)
c. Statement and Undertaking on FORM – 3
d. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No.**686065** dated **November 30, 2002** on **ANZ Grindlays Bank, New Delhi.**

We request that a patent may be granted to us for the said invention.

Dated this **13TH** day of **December, 2002.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

FORM 2 1263-02

The Patents Act, 1970
(39 of 1970)

16 DEC 2002

COMPLETE SPECIFICATION
(See Section 10)

DUPLICATE

AN IMPROVED PROCESS FOR THE PURIFICATION OF LEVOFLOXACIN HEMIHYDRATE

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to an improved process for the purification of levofloxacin hemihydrate, an antimicrobial compound .

Levofloxacin is chemically (S)-9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido [1,2,3de][1,4]benzoxazine-6-carboxylic acid, of structural formula I and is used for treating bacterial infection. It is a well known antibacterial agent, and is active against a broad spectrum of gram positive and gram negative bacteria. Levofloxacin is particularly more effective against Streptococcus and Staphylococcus strains of bacteria.

Levofloxacin exists as hemihydrate crystalline form and monohydrate form of structural formula II, as shown in the accompanied drawings, differing in a number of water molecules in the crystals, or as anhydrous crystals obtained by dehydrating these hemihydrates and monohydrates.

US Patent No. 5053407 describes a process for the production of levofloxacin which involves recrysallization of levofloxacin from a solvent mixture of ethanol and diethyl ether. The use of the solvent mixture causes the crystallization of levofloxacin monohydrate, together with the target levofloxacin hemihydrate form.

The conversion of this monohydrate into hemihydrate may be difficult to achieve in practice. Namely, when crystal water is removed from monohydrate and the anhydrous crystals thus obtained are allowed to take up moisture, only the original monohydrate is obtained. When levofloxacin is contaminated with the monohydrate, there is need of crystallization or recrystallization step till such contamination disappears.

Furthermore, anhydrous crystals obtained by removing crystal water cause blocking or sticking, and industrial operations with them become troublesome. Accordingly, a method of preparing a hydrated crystals is unsuitable as an industrial process.

The prior art approach was not suitable from commercial point of view because the desired products are not obtained in high purity and is more time consuming thus making the process complicated from industrial point of view.

To achieve high efficiency of reaction for industrial scale synthesis it is necessary minimizing monohydrate formed along with levofloxacin hemihydrates.

Thus the present invention provides a process which leads to the formation of levofloxacin hemihdyrate in highly pure form in less reaction time.

Under these circumstances, the present inventors have conducted extensive studies. As a result they have discovered that levofloxacin hemihydrate, free from monohydrate can be obtained by controlling the crystallization conditions. In addition, the inventors discovered that pure levofloxacin hemihydrate crystals, essentially free from monohydrate form is obtained by water treatment of about 10 minutes, after recovery of the solvents used.

Pure levofloxacin hemihydrate crystals are prepared by treating crude levofloxacin, with organic solvent, water or mixtures thereof, by heating and then cooled so as to induce crystallization.

Organic solvents comprises of solvents such as chlorinated hydrocarbons, hydrocarbons, esters or mixtures thereof.

Chlorinated hydrocarbons are selected from chloroform, dichloromethane, 1,2-dichloroethane or mixtures thereof. Among these solvents dichloromethane is most preferable.

Hydrocarbons are selected from of hexanes, cyclohexanes, toluene, or mixtures thereof.

Esters are selected from methyl acetate, ethyl acetate, or mixtures thereof. Preferably ethyl acetate is used.

The preferred embodiment of this aspect of the present invention comprises, treating crude levofloxacin with organic solvents, water or mixtures thereof, in the presence of a base such as triethylamine. The reaction mixture is heated to reflux temperature for about 0 to 10 hours. More preferably the heating temperature is 50-52°C for about 2 hours.

Further the process of the present invention comprises of cooling the above reaction mixture to 30-35°C, adding active charcoal and heating the solution to reflux temperature for about half an hour. The solution is filtered hot, followed by washing with dichloromethane, and its subsequent recovery. After the complete recovery of dichloromethane, water is added to maintain the moisture content to 0.90-1.00% . The obtained residue is washed with ethyl acetate to obtain pure (>99.5% HPLC purity) levofloxacin hemihydrate crystals.

While the present invention has been described in terms of its specific embodiments, certain modification and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

EXAMPLE

Levofloxacin crude (1.25 kg) was taken in dichloromethane (25 lit.) at ambient temperature, followed by adding ethylacetate (18.75 lit.). It was stirred , triethylamine (0.525 lit.) and water (0.75 lit.) were added. The reaction mixture was heated to reflux (50 –52 °C) for about 2 hours, and was cooled to 30 –35 °C, followed by active charcoal treatment. It was further heated to reflux temp for 30 minutes . Filtered hot through Hyflo bed and washed the bed with dichloromethane (5.0 lit.), followed by adding water (350 ml). The resulting slurry was cooled to 35 °, solid was filtered followed by washing with ethyl acetate. This results in levofloxacin hemihydrate more than 99.5 % pure by HPLC (RS method).

The physical data (elemental analysis, water content, X-Ray diffraction) of the levofloxacin hemihydrate obtained matches with the authentic samples of levofloxacin hemihydrate.

WE CLAIM:

1. A process for the purification of (S)-9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-di][1,4]-benzoxazine-6-carbxoylic acid hemihydrate of structural formula I as shown in accompanied drawings, which comprises of treating crude levofloxacin with organic solvent, water or mixtures thereof to produce pure levofloxacin hemihydrate .

2. The process of claim 1 wherein the reaction is carried out in the presence of a base.

3. The process of claim 1 wherein the reaction is carried out under heating conditions.

4. The process of claim 3 wherein the heating temperature ranges from about 50 to 52°C.

5. The process of claim 1 wherein organic solvent is selected from chlorinated hydrocarbons, hydrocarbons, esters or mixtures thereof.

6. The process of claim 5 wherein chlorinated hydrocarbons are selected from chloroform, dichloromethane, 1,2-dichloroethane or mixtures thereof.

7. The process of claim 6 wherein the said chlorinated hydrocarbon is dichloromethane.

8. The process of claim 5 wherein hydrocarbons are selected from hexanes, cyclohexanes, toluene or mixtures thereof.

9. The process of claim 5 wherein esters are selected from methyl acetate, ethyl acetate or mixtures thereof.

10. The process of claim 9 wherein the said ester is ethyl acetate.

11. The process of claim 3 further comprises of cooling the reaction mixture after the said reaction is completed.

12. The process of claim 11 wherein the cooling temperature ranges from about 30-35°C.

13. The process of claim 12 further comprises washing the obtained residue with organic solvent followed by its recovery.

14. The process of claim 13 wherein the said organic solvent is dichloromethane.

15. The process of claim 12 further comprises of adding water after complete recovery of dichloromethane, to obtain the slurry containing pure levofloxacin hemihydrate crystals.

16. The process of claim 15 further comprises of filtering the above slurry containing levofloxacin hemihydrate followed by washing with ethyl acetate.

17. The process for the preparation of pure (S)-9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-di][1,4]-benzoxazine-6-carbxoylic acid hemihydrate of structural formula I as shown in accompanied drawings, substantially as herein described and exemplified by the examples.

Dated this 13TH day of **December, 2002.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
COMPANY SECRETARY

ABSTRACT 1263-02

16 DEC 2002

The invention describes an improved process for the purification of levofloxacin hemihydrate which comprises treating crude levofloxacin with organic solvent, water or mixtures thereof by heating and then cooling the reaction mixture to obtain pure levofloxacin hemihydrate crystals essentially free of monohydrate crystals.

APLICATE

Ranbaxy Laboratories Limited

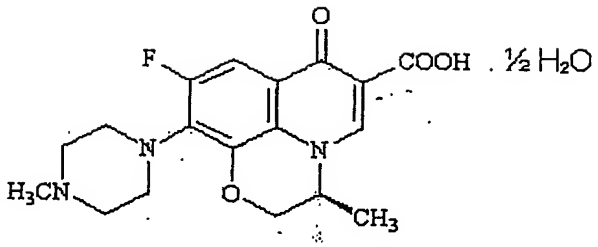
Application No.

No. of sheets = 02

Sheet 01 of 02

1263-02

16 DEC 2002



FORMULA I

DUPLICATE

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

Ranbaxy Laboratories Limited

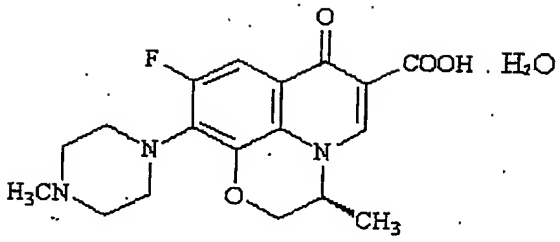
Application No.

No. of sheets = 02

Sheet 02 of 02

1263-02

16 DEC 2002



FORMULA II

DUPLICATE

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary